For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

Uniprogestin

1. Generic Name

Hydroxyprogesterone Injection IP

2. Qualitative and quantitative composition

Uniprogestin 250

Each ml contains: (1 ml ampoule)

Hydroxyprogesterone Caproate IP…….. 250 mg

Benzyl Alcohol IP (As Preservative) ….. 0.02 ml

Oily base …… q.s.

The excipients used are Benzyl benzoate and castor oil.

Uniprogestin 500

Each ml contains: (2 ml ampoule)

Hydroxyprogesterone Caproate IP…….. 250 mg

Benzyl Alcohol IP (As Preservative) ….. 0.02 ml

Oily base …… q.s.

The excipients used are Benzyl benzoate and castor oil.

3. Dosage form and strength

Dosage form: Solution for injection
Strength: 250 mg per 1 ml and 500 mg per 2ml

4. Clinical particulars

4.1 Therapeutic indication

- Uniprogestin is a progestin indicated to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth.
- To prevent premature birth and threatened abortion.

4.2 Posology and method of administration

- **Uniprogestin** (Single dose ampoule): Administer intramuscularly at a dose of 250 mg (1 mL) once weekly (every 7 days) or as directed by the Physician.
- Begin treatment between 16 weeks, 0 days and 20 weeks, 6 days of gestation
- Continue administration once weekly until week 37 (through 36 weeks, 6 days) of gestation or delivery, whichever occurs first

Method of administration: For Intramuscular (IM) injection only.

Do not use if solution is not clear or has suspended matter.

It should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if solid particles appear or if the solution is cloudy. Slow injection (over one minute or longer) is recommended.

4.3 Contraindications

Uniprogestin is contraindicated in women with a history of hypersensitivity to progestin or any of the excipients.

Do not use Uniprogestin in women with any of the following conditions:

- Current or history of thrombosis or thromboembolic disorders
- Known or suspected breast cancer, other hormone-sensitive cancer, or history of these conditions
- Undiagnosed abnormal vaginal bleeding unrelated to pregnancy
- Cholestatic jaundice of pregnancy
- Liver tumors, benign or malignant, or active liver disease
- Uncontrolled hypertension

4.4 Special warnings and precautions for use

Thromboembolic Disorders

Discontinue Uniprogestin if an arterial or deep venous thrombotic or thromboembolic event occurs.

Allergic Reactions

Allergic reactions, including urticaria, pruritus and angioedema, have been reported with use of Uniprogestin or with other products containing castor oil. Consider discontinuing the drug if such reactions occur.

Decrease in Glucose Tolerance

A decrease in glucose tolerance has been observed in some patients on progestin treatment. The mechanism of this decrease is not known. Carefully monitor prediabetic and diabetic women while they are receiving Uniprogestin**.**

Fluid Retention

Because progestational drugs may cause some degree of fluid retention, carefully monitor women with conditions that might be influenced by this effect (e.g., preeclampsia, epilepsy, migraine, asthma, cardiac or renal dysfunction). Require careful observation.

Depression

Monitor women who have a history of clinical depression and discontinue Uniprogestin if clinical depression recurs.

Jaundice

Carefully monitor women who develop jaundice while receiving Uniprogestin and consider whether the benefit of use warrants continuation.

Hypertension

Carefully monitor women who develop hypertension while receiving Uniprogestin and consider whether the benefit of use warrants continuation.

The pre-treatment physical examination should include examination of the breasts and pelvic organs and a Papanicolaou smear. In relation to irregular bleeding which does not respond predictably to the hormone therapy, non-functional causes should be borne in mind and adequate diagnostic measures instituted.

Patients who have a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.

4.5 Drugs interactions

Reported Invitro drug-drug interaction studies were conducted with Hydroxyprogesterone caproate. Hydroxyprogesterone caproate has minimal potential for CYP1A2, CYP2A6, and CYP2B6 related drug-drug interactions at the clinically relevant concentrations. In vitro data indicated that therapeutic concentration of hydroxyprogesterone caproate is not likely to inhibit the activity of CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4. The need for oral antidiabetics or insulin may change.

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy: *Pregnancy Category B.* There are no adequate and well-controlled studies of hydroxyprogesterone caproate use in women during the first trimester of pregnancy. Reported Data from a vehicle (placebo)-controlled clinical trial of 310 pregnant women who received hydroxyprogesterone caproate at weekly doses of 250 mg by intramuscular injection in their second and third trimesters, as well as long-term (2-5 years) follow-up safety data on 194 of their infants, did not demonstrate any teratogenic risks to infants from in utero exposure to hydroxyprogesterone caproate.

Reproduction studies have been performed in mice and rats at doses up to 95 and 5, respectively, times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to hydroxyprogesterone caproate.

Labor and Delivery: Hydroxyprogesterone caproate is not intended for use to stop active preterm labor. The effect of hydroxyprogesterone caproate in active labor is unknown.

Lactation: Discontinue hydroxyprogesterone at 37 weeks of gestation or upon delivery. Detectable amounts of progestins have been identified in the milk of mothers receiving progestin treatment. Many studies have found no adverse effects of progestins on breastfeeding performance, or on the health, growth, or development of the infant.

Risk Summary

Uniprogestin is indicated to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth. Fetal, neonatal, and maternal risks are discussed throughout labeling. Data from the Reported placebo-controlled clinical trial and the infant follow-up safety study did not show a difference in adverse developmental outcomes between children of Uniprogestin-treated women and children of control subjects. However, these data are insufficient to determine a drug-associated risk of adverse developmental outcomes as none of the Uniprogestin-treated women received the drug during the first trimester of pregnancy. In reported animal reproduction studies, intramuscular administration of hydroxyprogesterone

caproate to pregnant rats during gestation at doses 5 times the human dose equivalent based on a 60-kg human was not associated with adverse developmental outcomes**.**

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Animal Data

Reported reproduction studies of hydroxyprogesterone caproate administered to various animal species have been reported in the literature. In nonhuman primates, embryo lethality was reported in rhesus monkeys administered hydroxyprogesterone caproate up to 2.4 and 24 times the human dose equivalent, but not in cynomolgus monkeys administered hydroxyprogesterone caproate at doses up to 2.4 times the human dose equivalent, every 7 days between days 20 and 146 of gestation. There were no teratogenic effects in either strain of monkey. Reproduction studies have been performed in mice and rats at doses up to 95 and 5, respectively, times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to hydroxyprogesterone caproate.

Lactation: Discontinue hydroxyprogesterone at 37 weeks of gestation or upon delivery. Detectable amounts of progestins have been identified in the milk of mothers receiving progestin treatment. Many studies have found no adverse effects of progestins on breastfeeding performance, or on the health, growth, or development of the infant.

Risk Summary

Low levels of progestins are present in human milk with the use of progestin-containing products, including hydroxyprogesterone caproate. Published studies have reported no adverse effects of progestins on the breastfed child or on milk production.

Paediatric Use

Uniprogestin is not indicated for use in women under 16 years of age. Safety and effectiveness in patients less than 16 years of age have not been established. In reported data A small number of women under age 18 years were studied; safety and efficacy are expected to be the same in women aged 16 years and above as for users 18 years and older.

Hepatic Impairment

No studies have been conducted to examine the pharmacokinetics of Uniprogestin in patients with hepatic impairment. Uniprogestin is extensively metabolized and hepatic impairment may reduce the elimination of Uniprogestin.

4.7 Effects on ability to drive and use machines

Not Stated

4.8 Undesirable effects

For the most serious adverse reactions to the use of progestins, see *Warnings and Precaution).*

The following adverse reactions have been identified following use of hydroxyprogesterone caproate.

Body as a whole: Local injection site reactions (including erythema, urticaria, rash, irritation, hypersensitivity, warmth); fatigue; fever; hot flashes/flushes

- *Digestive disorders*: Vomiting
- *Infections*: Urinary tract infection
- *Nervous system disorders*: Headache, dizziness
- *Pregnancy, puerperium and perinatal conditions:* Cervical incompetence, premature rupture of membranes
- *Reproductive system and breast disorders:* Cervical dilation, shortened cervix
- *Respiratory disorders*: Dyspnea, chest discomfort
- *Skin*: Rash

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.

4.9 Overdose

There have been no reports of adverse events associated with overdosage of Hydroxyprogesterone Caproate in reported clinical trials. In the case of overdosage, the patient should be treated symptomatically.

5. Pharmacological properties

5.1 Mechanism of Action

Hydroxyprogesterone caproate is a synthetic progestin. The mechanism by which hydroxyprogesterone caproate reduces the risk of recurrent preterm birth is not known.

Hydroxyprogesterone caproate is an ester of the naturally occurring hydroxyprogesterone and possesses progesterone-like progestogenic effects such as antigonadotropic effects, the secretory transformation of the endometrium and thickening of the cervical mucus. The transformation of the endometrium facilitates the implantation of a fertilized ovum and creates favorable conditions for the maintenance of any pregnancy.

5.2 Pharmacodynamics properties

No specific pharmacodynamics studies were conducted with Uniprogestin.

Pharmacotherapeutic group: Pregnene-4 derivatives.

Hydroxyprogesterone caproate is a long-acting progestogen which causes secretory transformation of the endometrium at a dose of 250mg. The effect of hydroxyprogesterone caproate on the endometrium persists for about 10 days if an estrogen is administered at the same time. The mechanism by which hydroxyprogesterone reduces the risk of recurrent preterm birth is not known. Hydroxyprogesterone caproate is an ester of the naturally occurring hydroxyprogesterone and possesses progesterone-like progestogenic effects such as antigonadotropic effects, the secretory transformation of the endometrium and thickening of the cervical mucus. The transformation of the endometrium facilitates the implantation of a fertilized ovum and creates favorable conditions for the maintenance of any pregnancy.

In the case of parenteral administration the transformation dose of hydroxyprogesterone caproate is 250mg. The progestogen possesses only a minor inhibitory effect on LH secretion and no effect on the

Placental production of hormones like progesterone. Hydroxyprogesterone caproate has no estrogenic, androgenic, antiandrogenic or corticoid effects. Unlike the short-lived effect of progesterone, hydroxyprogesterone caproate possesses a distinct depot effect. For this reason, if a single intramuscular injection is performed when an estrogen is being administered at the same time, an effect on the endometrium lasting 10 days can be observed. The thermogenic effect of hydroxyprogesterone caproate is small. The retardant effect that all sexual hormones have on the anterior pituitary-hypothalamus system is relatively weak in the case of hydroxyprogesterone caproate: It inhibits neither the progesterone production in the corpus luteum phase nor hormone production in the placenta.

5.3 Pharmacokinetic properties

***Absorption**:*

Peak serum levels of hydroxyprogesterone caproate appeared after 3-7 days in non-pregnant female subjects following a single intramuscular injection of 1000 mg hydroxyprogesterone caproate. Based on pharmacokinetic analysis of five non-pregnant female subjects who received a single intramuscular administration of 1000 mg hydroxyprogesterone caproate, the mean (±SD) Cmax is estimated to be 27.8 (±5.3) ng/mL, and the Tmax is estimated to be 4.6 (±1.7) days. Once-weekly intramuscular administration of 1000 mg hydroxyprogesterone caproate to non-pregnant women resulted in trough concentration of 60.0 (±14) ng/mL after 13 weeks.

Female patients with a singleton pregnancy received intramuscular doses of 250 mg hydroxyprogesterone caproate for the reduction of preterm birth starting between 16 weeks 0 days and 20 weeks 6 days. All patients had blood drawn daily for 7 days to evaluate pharmacokinetics.

Table 4 Summary of Mean (Standard Deviation) Pharmacokinetic Parameters for Hydroxyprogesterone Caproate

Group (N)	Cmax (ng/mL)	Tmax (days)[a]	AUC(0-t)[b] (ng·hr/mL)
Group 1 (N=6)	5.0 (1.5)	5.5 (2.0-7.0)	571.4 (195.2)
Group 2 (N=8)	12.5 (3.9)	1.0 (0.9-1.9)	1269.6 (285.0)
Group 3 (N=11)	12.3 (4.9)	2.0 (1.0-3.0)	1268.0 (511.6)

In the reported study Blood was drawn daily for 7 days (1) starting 24 hours after the first dose between Weeks 16-20 (Group 1), (2) after a dose between Weeks 24-28 (Group 2), or (3) after a dose between Weeks 32-36 (Group 3)

[a] Reported as median (range)

[b] t = 7 days

For all three groups, peak concentration (Cmax) and area under the curve (AUC (1-7 days)) of the mono-hydroxylated metabolites were approximately 3-8-fold lower than the respective parameters for the parent drug, hydroxyprogesterone caproate. While di-hydroxylated and trihydroxylated metabolites were also detected in human plasma to a lesser extent, no meaningful quantitative results could be derived due to the absence of reference standards for these multiple hydroxylated metabolites. The relative activity and significance of these metabolites are not known.

The elimination half-life of hydroxyprogesterone caproate, as evaluated from 4 patients in the study who reached full-term in their pregnancies, was 16.4 (±3.6) days. The elimination half-life of the mono-hydroxylated metabolites was 19.7 (±6.2) days.

In a reported single-dose, open-label, randomized, parallel design bioavailability study in 120 healthy post-menopausal women, comparable systemic exposure of hydroxyprogesterone caproate was seen when Uniprogestin was administered subcutaneously with the auto-injector (1.1 mL) in the back of the upper arm and when Uniprogestin was dosed intramuscularly (1 mL) in the upper outer quadrant of the gluteus maximus.

Distribution*:* Hydroxyprogesterone caproate binds extensively to plasma proteins including albumin and corticosteroid binding globulins.

Metabolism*:* Reported vitro studies have shown that hydroxyprogesterone caproate can be metabolized by human hepatocytes, both by phase I and phase II reactions. Hydroxyprogesterone caproate undergoes extensive reduction, hydroxylation and conjugation. The conjugated metabolites include sulfated, glucuronidated and acetylated products. In vitro data indicate that the metabolism of hydroxyprogesterone caproate is predominantly mediated by CYP3A4 and CYP3A5. The in vitro data indicate that the caproate group is retained during metabolism of hydroxyprogesterone caproate. ***Excretion****:* Both conjugated metabolites and free steroids are excreted in the urine and feces, with the conjugated metabolites being prominent. Following intramuscular administration to pregnant women at 10-12 weeks gestation, approximately 50% of a dose was recovered in the feces and approximately 30% recovered in the urine. The elimination half-life of hydroxyprogesterone caproate was 7.8 (±3.0) days.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

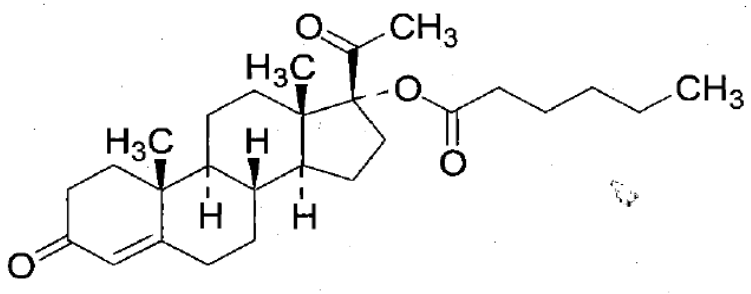
Carcinogenesis, Mutagenesis, Impairment of Fertility

Hydroxyprogesterone caproate has not been adequately evaluated for carcinogenicity.

No reproductive or developmental toxicity or impaired fertility was observed in a multigenerational study in rats. Hydroxyprogesterone caproate administered intramuscularly, at gestational exposures up to 5 times the recommended human dose, had no adverse effects on the parental (F0) dams, their developing offspring (F1), or the latter offspring's ability to produce a viable, normal second (F2) generation.

7. Description

Hydroxyprogesterone Caproate is Progestogen. Chemically it is 3, 20 –dioxopregn-4-en-17α-yl hexanoate. The empirical formula is $C_{27}H_{40}O_4$ and its molecular weight is 428.6 g/mol. The chemical structure of Hydroxyprogesterone Caproate is:



Hydroxyprogesterone caproate is a white or almost white, crystalline powder, odourless or almost odourless.

Hydroxyprogesterone Injection 250 mg and 500 mg are clear colourless to pale yellow solution. The excipients used are Benzyl benzoate and castor oil.

8 Pharmaceutical particulars

8.1 Incompatibilities

None Stated

8.2 Shelf-life

Do not use later than the date of expiry.

8.3 Packaging information

Uniprogestin 250 is packed in Blister contains one filled and labeled 1 ml glass ampoule with a sterile disposable Syringe with needle.

Uniprogestin 500 is packed in Blister contains one filled and labeled 2 ml glass ampoule with a sterile disposable Syringe with needle.

8.4 Storage and handing instructions

Store below 25°C, protect from light & moisture. Do not freeze.

Keep out of reach of children.

9. Patient Counselling Information

Uniprogestin
(Hydroxyprogesterone caproate injection)
For intramuscular use

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

• Keep this leaflet. You may need to read it again.

• If you have any further questions, ask your doctor or pharmacist.

• This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.

• If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 9.4.

What is in this leaflet?

9.1.What is Uniprogestin?

Uniprogestin is a prescription hormone medicine (progestin) used in women who are pregnant and who have delivered a baby too early (preterm) in the past. Uniprogestin is used in these

women to help lower the risk of having a preterm baby again. It is not known if Uniprogestin reduces the number of babies who are born with serious medical conditions or die shortly after birth. Uniprogestin is for women who:

- Are pregnant with one baby.
- Have had a preterm delivery of one baby in the past. Uniprogestin is not intended for use to stop active preterm labor. It is not known if Uniprogestin is safe and effective in women who have other risk factors for preterm birth. Uniprogestin is not for use in women under 16 years of age.

9.2 Who should not receive Uniprogestin?

Uniprogestin should not be used if you have:

- blood clots or other blood clotting problems now or in the past
- breast cancer or other hormone-sensitive cancers now or in the past
- unusual vaginal bleeding not related to your current pregnancy
- yellowing of your skin due to liver problems during your pregnancy
- liver problems, including liver tumors
- high blood pressure that is not controlled

What should you tell your healthcare provider before receiving Uniprogestin?

Before you receive Uniprogestin, tell your healthcare provider about all of your medical conditions, including if you have:

- A history of allergic reaction to hydroxyprogesterone caproate, castor oil, or any of the other ingredients in Uniprogestin. See the end of this Patient Information leaflet for a complete list of ingredients in Uniprogestin.
- Diabetes or pre-diabetes.
- Epilepsy (seizures).
- Migraine headaches.
- Asthma.
- Heart problems.
- Kidney problems.
- Depression.
- High blood pressure**.**

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Uniprogestin may affect the way other medicines work, and other medicines may affect how Uniprogestin works. Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

9.3 How should you receive Uniprogestin?

Do not give yourself Uniprogestin injections. A healthcare provider will give you the Uniprogestin injection 1 time each week (every 7 days) in the upper outer area of the buttocks as an injection into the muscle (intramuscular).

- You will start receiving Uniprogestin injections anytime from 16 weeks and 0 days of your pregnancy, up to 20 weeks and 6 days of your pregnancy.
- You will continue to receive Uniprogestin injections 1 time each week until week 37 (through 36 weeks and 6 days) of your pregnancy or when your baby is delivered, whichever comes first.

9.4 Possible side effects

Like all medicines, these tablets can cause side effects, although not everybody gets them. They may happen hours or days after you have taken the tablets. There is no clear information on how often side effects occur after taking this medicine. If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your health care provider.

Blood clots. Symptoms of a blood clot may include:

- leg swelling
- redness in your leg
- a spot on your leg that is warm to the touch
- leg pain that gets worse when you bend your foot

Call your healthcare provider right away if you get any of the symptoms above during treatment with Uniprogestin.

Allergic reactions. Symptoms of an allergic reaction may include:

- Hives, itching, swelling of the face

Call your healthcare provider right away if you get any of the symptoms above during treatment with Uniprogestin.

- Decrease in glucose (blood sugar) tolerance. Your healthcare provider will need to monitor your blood sugar while taking Uniprogestin if you have diabetes or pre-diabetes.
- Your body may hold too much fluid (fluid retention).
- Depression.
- Yellowing of your skin and the whites of your eyes (jaundice).
- High blood pressure.

The most common side effects of Uniprogestin include:

- pain, swelling, itching or a hard bump at the injection site
- hives
- itching
- nausea
- Diarrhea

Call your healthcare provider if you have the following at your injection site:

- increased pain over time
- oozing of blood or fluid
- swelling

Other side effects that may happen more often in women who receive Uniprogestin include:

- Miscarriage (pregnancy loss before 20 weeks of pregnancy)
- Stillbirth (fetal death occurring during or after the 20th week of pregnancy)
- Hospital admission for preterm labor
- Preeclampsia (high blood pressure and too much protein in your urine)
- Gestational hypertension (high blood pressure caused by pregnancy)
- Gestational diabetes
- Oligohydramnios (low amniotic fluid levels)

The most common adverse reactions that led to discontinuation are:

- A rash of round with sever itching and swelling
- Injection site pain/swelling
- Blood clots

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.

By reporting side effects, you can help provide more information on the safety of this medicine.

9.5 How to store Uniprogestin

Store below 25°C, protect from light & moisture. Do not freeze.

. Keep out of reach of children.

9.6 Contents of the pack and other information

Uniprogestin 250

Each ml of Uniprogestin contains: (1 ml ampoule)

Hydroxyprogesterone Caproate IP 250 mg as active ingredient

The excipients used are Benzyl Alcohol, Benzyl benzoate and castor oil.

Uniprogestin 500

Each ml of Uniprogestin contains (2 ml ampoule)

Hydroxyprogesterone Caproate IP 500 mg as active ingredient

The excipients used are Benzyl Alcohol, Benzyl benzoate and castor oil.

10. Details of manufacturer

Akums Drugs & Pharmaceuticals Ltd.
47 & 48, Sector-6A, I.I.E., SIDCUL, Ranipur, Haridwar-249 403.

11. Details of permission or licence number with date

97/UA/SC/P-2009 issued on 15.07.2016

12. Date of revision

Jan 2020

MARKETED BY

TORRENT PHARMACEUTICALS LTD.
IN/ Uniprogestin 250mg, 500 mg/Jan-20/02/PI